Supreme Court, U.S.
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No. 01-344

IN THE SUPREME COURT OF THE UNITED STATES

TOMMY G. THOMPSON,
SECRETARY OF HEALTH AND HUMAN SERVICES,
ET AL., PETITIONERS

v.

WESTERN STATES MEDICAL CENTER, ET AL.

ON WRIT OF CERTIORARI
TO THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

BRIEF FOR THE PETITIONERS

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QUESTION PRESENTED

The Food and Drug Administration Modernization Act of 1997 (FDAMA), 21 U.S.C. 353a (Supp. V 1999), provides a limited exemption from the new drug approval (and certain other) requirements of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. 301 et seq., for drugs compounded by pharmacists. The question presented is whether FDAMA's limitation of that exemption to pharmacists who do not solicit prescriptions for or advertise particular compounded drugs, 21 U.S.C. 353a(a) and (c) (Supp. V 1999), is consistent with the First Amendment.

PARTIES TO THE PROCEEDINGS

Petitioners are Tommy G. Thompson, Secretary of Health and Human Services, and Bernard A. Schwetz, Acting Principal Deputy Commissioner, United States Food and Drug Administration. Respondents are Western States Medical Center, Women's International Pharmacy, Health Pharmacy, Apothecure, College Pharmacy, Lakeside Pharmacy, and Wedgewood Village Pharmacy.

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OPINIONS BELOW

The opinion of the court of appeals (Pet. App. 1a-15a) is reported at 238 F.3d 1090. The opinion of the district court (Pet. App. 16a-59a) is reported at 69 F. Supp. 2d 1288. The opinion of the district court granting respondents' motion for a temporary restraining order (Pet. App. 60a-70a) is unreported.

JURISDICTION

The judgment of the court of appeals was entered on February 6, 2001. A petition for rehearing was denied on April 27, 2001 (Pet. App. 78a-79a). On July 15, 2001, Justice O'Connor extended the time within which to file a petition for a writ of certiorari to and including August 25, 2001. The petition was filed on August

24, 2001, and was granted on October 29, 2001. The jurisdiction of this Court rests on 28 U.S.C. 1254(1).

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

The First Amendment to the United States Constitution provides that "Congress shall make no law * * * abridging the freedom of speech." The pertinent provisions of the Food and Drug Administration Modernization Act of 1997, 21 U.S.C. 353a (Supp. V 1999), and the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 et seq., are reprinted in the appendix to the petition for a writ of certiorari. Pet. App. 80a-107a.

STATEMENT

1. a. The Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. 301 et seq., establishes a comprehensive scheme for the regulation of drug manufacturing, labeling, marketing, and distribution in order to protect the public health and safety. The FDCA defines a "new drug" as "[a]ny drug * * * not generally recognized * * * as safe and effective for use under the conditions prescribed." 21 U.S.C. 321(p)(1). The FDCA generally requires that, before a new drug may be introduced into interstate commerce, the manufacturer or distributor must obtain the approval of the Secretary of Health and Human Services, acting through the Food and Drug Administration (FDA). See 21 U.S.C. 355(a), 331(d). To obtain that approval, the manufacturer or distributor must demonstrate to the FDA's satisfaction that the drug is both safe and effective for each intended use. See 21 U.S.C. 355(b) (1994 & Supp. V 1999); Weinberger v. Hynson, Westcott & Dunning, Inc., 412

U.S. 609, 613 (1973). The prohibition on introducing new drugs that have not been approved by the FDA applies to all new drugs except those for which Congress has created an exemption. See United States v. Rutherford, 442 U.S. 544, 551 (1979).

The FDCA also imposes standards for the manufacturing and labeling of drugs to ensure that manufacturing processes and drug ingredients are safe and effective and that physicians and consumers have adequate information about drug contents, uses, and effects. See 21 U.S.C. 351, 352 (1994 & Supp. V 1999). The FDCA prohibits the sale and distribution of "adulterated" or "misbranded" drugs. See 21 U.S.C. 331 (1994 & Supp. V 1999).

In addition, to facilitate regulatory oversight, the FDCA imposes registration, inspection, and reporting requirements on drug manufacturers. See 21 U.S.C. 360 (1994 & Supp. V 1999) (requiring drug manufacturers to register with the Secretary); 21 U.S.C. 360(h) (subjecting drug manufacturers to at least one government inspection every two years); 21 U.S.C. 360(j) (1994 & Supp. V 1999) (requiring each registered drug manufacturer to "file with the Secretary a list of all drugs" that it manufactures for commercial distribution).

The FDCA contains a limited exemption from its registration and some of its inspection requirements for pharmacies that comply with state regulations and dispense drugs "upon prescriptions of practitioners licensed to administer such drugs" and that do not "manufacture" or "compound" drugs other than in "the regular course of their business of dispensing or selling drugs * * * at retail."

21 U.S.C. 360(g)(1), 374(a)(2)(A). There is no general exemption for pharmacies, however, from the FDCA's new drug approval, misbranding, and adulteration provisions. 21 U.S.C. 351, 352, 355 (1994 & Supp. V 1999); Pet. App. 72a (1992 FDA Compliance Policy Guide).

b. Compounding is a process by which a pharmacist "combines, mixes, or alters ingredients to create a certain medication for a patient." Professionals & Patients for Customized Care v. Shalala, 847 F. Supp. 1359, 1361 (S.D. Tex. 1994), aff'd, 56 F.3d 592 (5th Cir. 1995). The process encompasses a range of pharmacy activities, including the modification of approved drugs "to provide medications that are not commercially available, such as diluted dosages for children, or to alter the form of a medication for easier consumption." Ibid.

When a pharmacy compounds a drug, the pharmacy creates a "new drug" because the compounded product is not "generally recognized, among experts * * *, as safe and effective." See 21 U.S.C. 321(p)(1). A drug that differs in any material way (including in composition, effect, or intended use) from an approved drug is a new drug that must independently be established to be safe and effective. See United States v. Generix Drug Corp., 460 U.S. 453, 460-461 (1983) (determination whether a product is a new drug takes into account both active and inactive ingredients); 21 C.F.R. 310.3(h) (discussing factors that make a drug a "new drug"). Even a drug that is identical to an approved product is a new drug that must be independently established as safe and effective if it is

produced by a different manufacturer. See USV Pharm. Corp. v. Weinberger, 412 U.S. 655, 664 (1973) ("[Section 355] when applied to [a new drug application] is personal to the manufacturer who files it. Section [355], in other words, addresses itself to drugs as individual products."); Pharmanex v. Shalala, 221 F.3d 1151, 1157 (10th Cir. 2000) (the new drug approval process is manufacturer-specific). A newly created, customized compounded drug will not have been subjected to the controlled clinical trials that are necessary to establish its safety and effectiveness. See Hynson, Westcott & Dunning, 412 U.S. at 630; Weinberger v. Bentex Pharm., Inc., 412 U.S. 645, 652 (1973). Although the prescribing physician presumably believes the compounded product is appropriate for the patient receiving the prescription, neither the impressions of practicing physicians nor the fact that a number of physicians throughout the country prescribe a compounded product is sufficient to establish that it is generally recognized as safe and effective. See Hynson, Westcott & Dunning, 412 U.S. at 630; United States v. Sene X Eleemosynary Corp., 479 F. Supp. 970, 977 (S.D. Fla. 1979), aff'd, [1982-1983 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) ¶ 38,207 (11th Cir. Jan. 12, 1983).

For those reasons, prior to the enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115, 111 Stat. 2296, several courts of appeals had confirmed that compounded drugs are "new drugs" subject to the FDCA's premarket approval requirements. See Professionals & Patients for Customized Care v. Shalala, 56 F.3d 592, 593 n.3 (5th Cir. 1995); United

States v. Algon Chem. Inc., 879 F.2d 1154, 1158 (3d Cir. 1989); United States v. 9/1 Kg. Containers, 854 F.2d 173, 179 (7th Cir. 1988); see also United States v. Baxter Healthcare Corp., 901 F.2d 1401, 1410-1411 (7th Cir. 1990) (reconstitution and freezing of already approved drug creates new drug). Introduction of compounded drugs into interstate commerce without the approval of the FDA was thus illegal before enactment of FDAMA, see Professionals & Patients, 56 F.3d at 593 n.3; Pet. App. 72a, and it remains illegal today unless the requirements in Section 353a are satisfied.

The FDA nevertheless recognized that compounding can serve an important public purpose for which the health benefits outweigh the risks if the compounding is performed in response to a valid prescription in order to meet the medical needs of an individual patient for whom commercially available drugs are inadequate. See Pet. App. 71a. Therefore, "the FDA as a matter of policy [did] not historically [bring] enforcement actions against pharmacies engaged in traditional compounding." 56 F.3d at 593 n.3.

The FDA did take action, however, when compounding was outside the scope of normal pharmacy practice and compounded drugs were mass-produced and distributed in a manner tantamount to the manufacture of unapproved new drugs. See Pet. App. 73a-74a. The FDA issued warning letters, see id. at 73a, and sometimes brought judicial enforcement actions against pharmacies that engaged in drug manufacturing under the guise of compounding. E.g., Sene X, 479 F. Supp. at 978; Cedars North Towers Pharmacy, Inc. v. United

States, [1978-79 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) ¶ 38,200, at 38,828 (S.D. Fla. Aug. 28, 1978).

Among the factors that the FDA considered in determining whether a pharmacy was engaged in conduct tantamount to manufacturing drugs rather than in traditional compounding were whether the pharmacy was "[s]oliciting business (e.g., promoting, advertising, or using sales persons) to compound specific drug products, product classes, or therapeutic classes of drug products." Pet. App. 76a. Other considerations included the extent to which the pharmacy was compounding drug products that were essentially copies of a commercially available drug product, was compounding drugs in advance of receiving valid prescriptions, or was distributing compounded products out of State. Id. at 76a-77a.

2. Congress addressed the compounding issue when it enacted FDAMA in 1997. The section of FDAMA at issue in this case, now codified at 21 U.S.C. 353a (Supp. V 1999), was intended to "bring the legal status of compounding in line with FDA's longstanding enforcement policy of regulating only drug manufacturing, not ordinary pharmacy compounding." 143 Cong. Rec. S9839 (daily ed. Sept. 24, 1997) (statement of Sen. Kennedy). Section 353a seeks to "ensure continued availability of compounded drug products as a component of individualized therapy, while limiting the scope of compounding so as to prevent manufacturing under the guise of compounding." H.R. Conf. Rep. No. 399, 105th Cong., 1st Sess. 94 (1997); accord S. Rep. No. 43, 105th Cong., 1st Sess. 67 (1997).

Rather than leaving to the enforcement discretion of the FDA the determination of when compounding should be permitted, Congress chose to delineate in the FDCA itself the limited circumstances under which pharmacy compounding would be exempt as a matter of law from certain requirements that apply to drug manufacturers. Thus, if specified conditions are met, Section 353a exempts compounded drug products from the FDCA's provisions governing new drug approval, good manufacturing practice, and adequate directions for use. Under those conditions, which echo the FDA's pre-1997 approach to compounding, (1) the compounding must be performed by a licensed pharmacist or physician based on a valid prescription made by a licensed practitioner, see 21 U.S.C. 353a(a)(1) (Supp. V 1999); (2) the compounding must use only ingredients that comply with various quality-control standards, see 21 U.S.C. 353a(b)(1)(A) and (B) (Supp. V 1999); (3) the compounded product may not be a drug product identified by regulation as presenting difficulties for compounding that would adversely affect safety or efficacy, see 21 U.S.C. 353a(b)(3)(A) (Supp. V 1999); (4) the compounding may not produce a drug that has been withdrawn from the market for safety reasons, see 21 U.S.C. 353a(b)(1)(C) (Supp. V 1999); and (5) the pharmacist may not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product, see 21 U.S.C. 353a(b)(1)(D), 353a(b)(2) (Supp. V 1999). FDAMA also limits the total volume of compounded drug products that a pharmacy may

distribute out of State. See 21 U.S.C. 353a(b)(3)(B) (Supp. V 1999).

In addition, FDAMA makes the exemption of compounded drugs from the specified FDCA requirements contingent upon the pharmacy's compliance with limitations on advertising and promotion of compounded drug products. Section 353a(a) exempts pharmacy compounding from the new drug approval and other requirements only if the compounded drug is produced "based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient." 21 U.S.C. 353a(a) (Supp. V 1999). Section 353a(c) further provides that a pharmacy is entitled to the exemption only if it "does not advertise or promote the compounding of any particular drug, class of drug, or type of drug." 21 U.S.C. 353a(c) (Supp. V 1999). The advertising limitation does not, however, prevent the pharmacy from advertising that it performs compounding services generally. 21 U.S.C. 353a(c) (Supp. V 1999).

3. In November 1998, shortly before the relevant provisions of FDAMA took effect, respondent pharmacies, which regularly compound drugs in significant quantities, commenced this suit in the United States District Court for the District of Nevada against the Secretary of Health and Human Services and the Commissioner of the FDA. Respondents sought a declaratory judgment that Sections 353a(a) and (c) violate the First Amendment and an order enjoining enforcement of those provisions against them.

The district court initially granted respondents a temporary restraining order that enjoined the government from enforcing Section 353a(c). Pet. App. 60a-70a. The parties subsequently filed cross-motions for summary judgment. The district court, concluding that Sections 353a(a) and (c) violate the First Amendment, granted respondents' motion, denied the government's motion, and permanently enjoined the FDA from enforcing the solicitation and advertising restrictions in Sections 353a(a) and (c). Pet. App. 16a-57a. The court further held that the restrictions were severable from the remainder of Section 353a. Id. at 57a-59a.

4. The United States Court of Appeals for the Ninth Circuit affirmed in part and reversed in part. Pet. App. 1a-15a.

a. Applying the four-part test enunciated in Central Hudson Gas & Electric Corp. v. Public Service Commission, 447 U.S. 557 (1980), for determining the constitutionality of regulation of commercial speech, the court of appeals affirmed the district court's holding that Sections 353a(a) and (c) violate the First Amendment. Pet. App. 4a-12a.

Because the government did not contest that the advertising and solicitation limitations in Section 353a apply to lawful, non-misleading speech, the court of appeals began its analysis with the second element in the Central Hudson analysis -- whether the governmental interests that underlie Section 353a's solicitation and advertising conditions are substantial. Pet. App. 5a. The court recognized that the government has substantial interests in

"protecting the public health and safety" and "preserving the integrity of the drug approval process." Pet. App. 5a. The court also recognized that "[t]he government's effort to balance competing goals can be a substantial interest." Id. at 6a. The court concluded, however, that the government had not demonstrated that "its interest in striking a balance between ensuring compounding availability and limiting widespread compounding is substantial." Id. at 7a. The court reached that conclusion because, in its view, "[t]here is insufficient evidence in the record to conclude that the government has a substantial interest in preventing widespread compounding." Ibid.

Turning to the third step in the Central Hudson analysis, the court held that the solicitation and advertising limitations in Section 353a do not directly advance either of the asserted interests that the court did find to be substantial -- protecting the public health and safety and preserving the integrity of the new drug approval process. Pet. App. 7a-10a. The court reasoned that the government "has not offered evidence or arguments to explain sufficiently why such restrictions will reduce the type of consumption of compounded drugs that is harmful, and even admits that it has a substantial interest in ensuring the availability of compounded drugs." Id. at 7a-8a. The court also concluded that, "[w]ithout the advertising restrictions, other safeguards exist to protect the public." Id. at 8a (citing 21 U.S.C. 353a(a) (requiring valid prescription for compounded drug products), 353a(b)(1) (limiting substances that pharmacists may use in

compounded products), and 353a(b)(1)(D) (Supp. V 1999) (preventing pharmacists from regularly compounding drugs that are essentially copies of commercially available products)).

In addition, relying on Rubin v. Coors Brewing Co., 514 U.S. 476 (1995), and Greater New Orleans Broadcasting Ass'n v. United States, 527 U.S. 173 (1999), the court concluded that Section 353a "is so riddled with exceptions that it is unlikely that the speech restrictions would actually succeed in depressing the volume of compounded drugs." Pet. App. 9a. The court observed that "pharmacists can advertise their compounding services and promote their skills at medical trade events so long as they do not promote the compounding of any particular drug," and that a pharmacist may call a physician and recommend a compounded drug if a patient comes in with a prescription for a commercial drug and provides information to the pharmacist that indicates that the patient might require a compounded product. Ibid. In addition, the court stated that FDAMA permits compounded drugs to constitute 5% of the total interstate distributions and 100% of the total intrastate distributions by a particular pharmacy. Ibid. (citing 21 U.S.C. 353a(b)(3) (Supp. V 1999)).

The court next addressed the fourth Central Hudson factor and concluded that the advertising and solicitation restrictions "are more extensive than necessary to achieve the asserted government interest." Pet. App. 10a. The court suggested that, instead of limiting advertising, the FDA could require disclaimers stating that the compounded drugs being advertised had not been subjected

to the FDA's approval process. Ibid. The court also offered the alternative of requiring all compounded drugs, including those created on an individual basis as part of the traditional practice of pharmacy, to undergo the safety and effectiveness testing required for new drugs under the FDCA. Ibid. The court rejected the government's argument that those alternatives would not address the government's interest in drawing a workable distinction between traditional, patient-based compounding and the manufacturing of new drugs, because the court had already determined that the government's interest in balancing those competing goals is not substantial. Id. at 11a.

b. Although the court of appeals affirmed the district court's judgment insofar as it held that the solicitation and advertising conditions in Section 353a violate the First Amendment, the court, accepting the government's submission, reversed the district court's decision to sever those provisions from the rest of Section 353a. Pet. App. 12a-15a. The court reasoned that "Congress intended to provide access to compounded drugs while preventing pharmacies from making an end run around the FDA's drug manufacturing requirements." Id. at 12a. Because "Congress meant to exempt compounding pharmacists from FDCA requirements only in return for a prohibition on the promotion of specific compounded drugs," the court concluded that the solicitation and advertising restrictions could not be severed from the rest of Section 353a. Id. at 13a-14a. Accordingly, the court invalidated Section 353a in its entirety. Id. at 15a.

SUMMARY OF ARGUMENT

A. Section 353a attempts to achieve two important but competing goals. It seeks to preserve the integrity of the FDCA's new drug approval process, which protects the public health by ensuring that new drugs are not widely distributed in interstate commerce unless they are first proven safe and effective. It also seeks to preserve the availability of compounded drugs for those individual patients who, for particularized medical reasons, cannot use commercial products that have been approved by the FDA.

Based on its long experience with the regulation of drugs, Congress concluded that proof of the safety and effectiveness of a new drug must be established by rigorous, scientifically valid studies rather than the impressions of individual doctors, who cannot by themselves compile and master the necessary information. Historical experience also convinced Congress that a premarket approval requirement is necessary to ensure that those who promote and distribute new drugs, and realize profits from their distribution, undertake the investigations necessary to establish safety and effectiveness.

At the same time, Congress recognized that it is also important to ensure that safe and effective drug treatments are in fact available, and that goal is also reflected in the FDCA. Consistent with that goal, the FDA historically refrained from enforcing the new drug approval requirements against pharmacies that compounded drugs in response to valid prescriptions to meet the medical needs of individual patients. That policy recognized

that compounding in response to individual medical needs is a traditional element of the practice of pharmacy that may have important health benefits, but pharmacies often will be unable to bear the burden and expense necessary to demonstrate to the FDA the safety and effectiveness of the compounded drugs before they are sold because of the limited market for them.

Experience showed, however, that some compounding was being conducted in a manner that threatened the safeguarding function of the new drug approval process. Some pharmacies were compounding outside the scope of normal pharmacy practice and mass-producing and distributing compounded drugs in a manner tantamount to the manufacture of new drugs. Compounding on that scale exposed significant numbers of people to the health and safety risks that had prompted enactment of the new drug approval requirements in the first place. Moreover, such compounding threatened the integrity and efficacy of the new drug approval process by making it less likely that manufacturers would have the requisite incentive to demonstrate that their new drugs are safe and effective for their intended uses. Pharmacies could mass-produce a particular drug product, stimulate demand for the product through soliciting and advertising, and thereby effectively manufacture and introduce the drug into interstate commerce without complying with the approval requirements. That practice would significantly reduce the incentives of manufacturers to bear the cost of establishing that the drugs they seek to market are safe and effective, because a manufacturer could obtain a pharmacy license and establish a

pharmacy entity to mass-produce drugs through compounding and thus circumvent the premarket approval requirements. Before enactment of Section 353a, the FDA therefore took enforcement actions against pharmacies that were manufacturing under the guise of compounding.

When Congress enacted Section 353a, it sought to achieve essentially the same balance of interests that the FDA had pursued through its enforcement policy - ensuring the continued availability of compounding to address the particularized needs of individual patients in cases in which it would be impractical to require a demonstration to the FDA of safety and effectiveness, while limiting the scope of compounding to prevent unregulated manufacturing that would threaten the integrity of the premarket approval process and undermine the FDCA regulatory scheme. Congress's effort to balance those two independently compelling but competing interests is itself a substantial governmental interest.

B. Section 353a directly and materially advances that substantial interest. Under certain conditions, Section 353a exempts compounded products from the FDCA's provisions governing new drug approval, good manufacturing practice, and adequate directions for use. The conditions at issue here are the limitations on the solicitation of prescriptions for and advertising of particular compounded drugs. Although those conditions restrict promotion of particular drugs, they do not restrict promotion of the compounding service in any other way. The specific solicitation and advertising conditions advance the government's interest because promotion of particular drugs

reasonably distinguishes drug manufacturing that should be subject to the premarket approval process from compounding in response to individual medical needs.

Traditional compounding involves the provision of a service in response to a physician's prescription and an individual patient's particular medical needs. Advertising the specific products created in the provision of that service (as opposed to advertising the compounding service itself) is not necessary to or characteristic of traditional compounding by a pharmacy. Drug manufacturing, in contrast, is the mass production of a homogenized product, typically for a substantial market, and advertising of particular drugs is typically a critical component of a successful manufacturing business. Restricting the compounding exemption to compounded products that are not subject to promotional activities characteristic of manufacturing ensures that the exemption does not create a loophole that would undermine the new drug approval process.

Limiting the exemption from the regulatory approval process to compounded drugs that are not advertised also reflects Congress's judgment in enacting the FDCA that the public health is best served when those who develop, distribute, and promote new drugs prove that those drugs are safe and effective. By preventing circumvention of the new drug approval requirements, the promotion limitations preserve the incentives for drug manufacturers to undertake the studies necessary to demonstrate that new drugs are safe and effective. Conditioning the exemption from the drug

approval requirements on whether a compounder promotes particular drugs is also consistent with the role that advertising and other promotional material have long played in determining the scope of regulation under the FDCA. For example, promotional activity has been an important consideration by the FDA in determining both whether a particular product is a drug subject to regulation under the FDCA and whether a new drug or a supplemental new drug application is required for a particular drug product.

The court of appeals therefore erred in concluding that the advertising and solicitation conditions on the availability of the exemption under Section 353a do not advance the government's interests. The other conditions on the availability of the exemption do not, as the court believed, provide adequate safeguards to protect the public. Nor do other provisions in Section 353a undermine the effectiveness of the advertising and solicitation limitations. Indeed, those provisions serve different purposes and ensure that the limitations are appropriately tailored to the government's interests.

C. The advertising and solicitation conditions on the availability of the exemption under Section 353a are carefully crafted so as to be no more extensive than necessary to advance the government's goals. They do not impose a prohibition on speech: a pharmacy that wishes to mass-produce a particular drug product and promote that product by advertising or by soliciting prescriptions can do so by complying with the premarket approval requirements that apply to other drug manufacturers.

The conditions on the availability of the exemption are also tailored to accommodate commercial speech attendant to compounding within the traditional practice of pharmacy. Section 353a(c) permits a pharmacy to advertise and promote its general compounding services. That kind of advertising promotes the availability of compounding in response to individual medical needs and does not threaten the integrity of the new drug approval process. Section 353a(a) permits compounding in limited quantities in anticipation of a valid prescription when that compounding is based on an established relationship among the pharmacist, the practitioner and the patient. It also permits a pharmacist to call a physician and recommend a compounded drug if a patient seeks to fill a prescription for a commercial drug and provides information that leads the pharmacist to conclude that a compounded product is required. Both of those practices are consistent with traditional compounding by a pharmacy in response to particularized medical needs and do not compromise the new drug approval requirements.

Finally, the alternatives to the advertising and solicitation limitations suggested by the court of appeals would not advance, but would undermine, the government's interests. Permitting promotion of compounded drugs provided they include disclaimers indicating that they have not been subject to premarket approval by the FDA would undermine the premarket approval process and would be fundamentally inconsistent with the protective framework of the FDCA. The other alternative offered by the court of appeals -- requiring premarket approval for all compounded drugs, even those

customized to meet the medical needs of specific patients -- would eliminate the availability of those products because demand for them is not sufficient to support the costs of the premarket approval process.

ARGUMENT

FDAMA'S LIMITED EXEMPTION FROM THE NEW DRUG APPROVAL REQUIREMENTS FOR DRUGS COMPOUNDED BY PHARMACISTS WHO DO NOT SOLICIT PRESCRIPTIONS FOR OR ADVERTISE PARTICULAR COMPOUNDED DRUGS IS CONSISTENT WITH THE FIRST AMENDMENT

Since 1938, the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. 301 et seq., has prohibited the introduction into interstate commerce of a new drug without prior approval of the Food and Drug Administration (FDA). 21 U.S.C. 355(a). In the Food and Drug Administration Modernization Act of 1997 (FDAMA), Congress provided a limited exemption from the new drug approval and certain related requirements of the FDCA for drugs compounded by pharmacists. See 21 U.S.C. 353a (Supp. V 1999). In this case, the United States Court of Appeals for the Ninth Circuit held that the solicitation and advertising limitations that Congress adopted as conditions on the availability of that exemption violate the First Amendment. Contrary to the Ninth Circuit's conclusion, the limitations on the exemption provided by Section 353a are fully consistent with the First Amendment.[1]

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[1] The government agrees with the court of appeals' conclusion (Pet. App. 12a-15a) that, if the solicitation and advertising provisions in Sections 353a(a) and (c) are unconstitutional, they are not severable from the remainder of Section 353a. For that reason, the government did not seek this Court's review of the severability issue. Respondents did not raise the issue in their brief in opposition, and they did not file a cross-petition for a writ of certiorari on the issue. The severability question is

In Central Hudson Gas & Electric Corp. v. Public Service Commission, 447 U.S. 557 (1980), this Court enunciated a four-part inquiry to determine the constitutionality under the First Amendment of government regulation of commercial speech: first, whether the speech "accurately inform[s] the public about lawful [commercial] activity," id. at 563; second, "whether the asserted governmental interest [underlying the speech regulation] is substantial," id. at 566; third, "whether the regulation directly advances the governmental interest asserted," ibid.; and, finally, "whether it is not more extensive than is necessary to serve that interest" (ibid.).

With respect to the first part of the Central Hudson inquiry, the government assumes that respondents' advertisements would be accurate and concern an activity that is otherwise lawful under the carefully circumscribed exemption that Congress has established for compounding. It is important, however, to stress that this case, unlike most commercial speech cases, does not involve a restriction on advertising that has been imposed in connection with an activity that the government otherwise has declined to prohibit. Before 1997, the introduction of compounded new drugs into interstate commerce - like the introduction of all other unapproved new drugs - was unlawful in all circumstances. In enacting Section 353a, Congress created an exemption to that generally applicable prohibition on the distribution of new drugs, but conditioned that

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therefore not before the Court. See, e.g., Bates v. United States, 522 U.S. 23, 32 n.7 (1997).

exemption on compliance with a number of requirements, including restrictions on solicitation and advertising. As the court of appeals explained, Congress "intended to provide access to compounded drugs while preventing pharmacies from making an end run around the FDA's drug manufacturing requirements." Pet. App. 12a. Congress therefore "meant to exempt compounding pharmacists from FDCA requirements only in return for a prohibition on the promotion of specific compounded drugs." Id. at 13a-14a. That is to say, but for the advertising restrictions in Section 353a, the relevant commercial conduct - the sale of new drugs that have not been shown to be safe and effective - would be (and is) prohibited.

Accordingly, this case is not one in which the government generally permits certain conduct and asserts a hypothetical (but uninvoked) "greater power" to prohibit the advertised conduct as a justification for exercising the "lesser power" of restricting the advertising of that conduct. See 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 510-513 (1996) (plurality opinion). Instead, Congress has exercised the "greater power" to prohibit the distribution of unapproved new drugs, and has permitted an exception to that prohibition only on compliance with various conditions, including restrictions on the solicitation and advertising of that otherwise unlawful commercial activity. The question, then, is whether Congress's inclusion of limitations on solicitation and advertising among the conditions on the availability of the exemption from certain of the FDCA's requirements satisfies the remaining three Central Hudson factors.

A. Substantial Governmental Interests Underlie Section 353a

In enacting Section 353a, Congress attempted to balance two goals, each of which is substantial. First, Congress sought to preserve the effectiveness and integrity of the FDCA's new drug approval process and the protection of the public health that it provides. Second, Congress sought to preserve the availability of compounded drugs for those individual patients who, for particularized medical reasons, cannot use commercially available products that have been approved by the FDA. Achieving the proper balance between those two independently compelling but competing interests is itself a substantial governmental interest.

1. There is a substantial governmental interest in protecting the integrity of the FDCA's new drug approval process

As both Congress and this Court have recognized, the widespread distribution of drugs that have not been shown to be safe and effective poses significant health risks. See United States v. Rutherford, 442 U.S. 544, 556-557 (1979); Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609, 622 (1973). The FDCA's new drug approval process is the culmination of a century of congressional efforts to advance the substantial interest in preventing those risks.

In the 19th century, the United States, which lacked laws and regulations of the sort that were in place in European countries, was plagued by substandard and contaminated drugs. Injuries from such drugs, such as a contaminated diphtheria vaccine that caused the death of a dozen children in 1902, eventually led to enactment of the Pure Food and Drugs Act of 1906, ch. 3915, 34 Stat. 768,

which prohibited interstate shipment of adulterated or misbranded drugs. See W.F. Janssen, Outline of the History of U.S. Drug Regulation and Labeling, 36 Food, Drug & Cosm. L.J. 420, 422-425 (1981). The 1906 Act, however, proved insufficient to ensure that marketed drugs were safe for use. Perhaps the most notorious example of that insufficiency was the Elixir Sulfanilamide tragedy of 1937. A company that had marketed sulfanilamide in capsule and tablet form began marketing the drug in a liquid form without adequately testing the safety of the liquid in which the sulfanilamide was dissolved. Before the drug could be recalled, 107 people, mostly children, died from using the product. See Elixir Sulfanilamide, S. Doc. 124, 75th Cong., 2d Session (1937); V. Henry, Problems with Pharmaceutical Regulation in the United States, 14 J. Leg. Med. 617, 619 (1993).

Congress enacted the FDCA in 1938 based on the historical experience demonstrating that manufacturer self-interest and physician screening were insufficient to protect the public from the dangers of widespread distribution of unsafe drugs. See Act of June 25, 1938, ch. 675, 52 Stat. 1040. At the heart of the new law was the new drug approval requirement -- that the manufacturer or distributor of a new drug must obtain approval from the FDA before introducing the new drug into interstate commerce. § 505(a), 52 Stat. 1052 (now codified as amended at 21 U.S.C. 355(a)).

Further experience revealed, however, that the preapproval requirements in the 1938 Act were still not sufficient to protect the public health and safety. One problem was that the Act

required proof only that a new drug was safe for its intended uses and not that it was effective for those uses. As a result, the FDA was forced to approve many drugs for general distribution even when there was no evidence that they would produce the therapeutic benefits claimed by their manufacturers. See S. Rep. No. 1744, 87th Cong., 2d Sess. Pt. 1, at 15-16 (1962); Drug Industry Antitrust Act: Hearings on S. 1552 Before the Subcomm. on Antitrust and Monopoly of the Senate Comm. on the Judiciary, Pt. 5, 87th Cong., 1st Sess. 2583-2585 (1961) (testimony of Abraham Ribicoff, Secretary of Health, Education, and Welfare). Because hundreds of new drugs were introduced each year, and information about their effectiveness took considerable time to develop and (when published at all) was scattered among hundreds of medical journals, physicians were unable to ascertain whether the drugs they were prescribing were effective. See S. Rep. No. 1744, supra, Pt. 1, at 37 (views of Sens. Kefauver, Carroll, Dodd, Hart, and Long); S. Rep. No. 448, 87th Cong., 1st Sess. 171 (1961); 108 Cong. Rec. 19,925-19,926 (1962); Warner-Lambert Co. v. Heckler, 787 F.2d 147, 156 (3d Cir. 1986). Prescription of ineffective drugs could have serious harmful consequences because, when an ineffective drug was prescribed, it usually replaced an older but effective drug. See S. Rep. No. 1744, supra, Pt. 1, at 37; see also Rutherford, 442 U.S. at 556-557 & n.13 (discussing danger that patients who use ineffective drugs will, as a consequence, delay or forgo use of effective drugs or other treatment).

Another problem with the 1938 Act was that a new drug application became effective automatically after 180 days if the FDA took no action. See S. Rep. No. 1744, supra, Pt. 1, at 40. Because of the automatic approval provision and the lack of independent and objective clinical studies to guide FDA physicians in evaluating new drugs, many drugs were released for distribution that were subsequently revealed to have serious (and sometimes deadly) side effects. See id. at 43. The possible dangers of automatic approval were graphically illustrat the thalidomide experience, in which reports of serious birth defe caused by the use of thalidomide in Europe surfaced shortly before he automatic approval requirement might have forced the FDA to permit widespread distribution of the drug in the United States. See id. at 40-43.

The Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780, addressed those problems by strengthening the new drug approval process. The amendments eliminated the automatic approval provision and required manufacturers and distributors to demonstrate not only the safety but also the effectiveness of new drugs. Under the amended provisions, a new drug may not be introduced (or delivered for introduction) into interstate commerce until the manufacturer or distributor obtains the FDA's affirmative approval by establishing that the drug is safe and effective for each of its intended uses. See 21 U.S.C. 321(p), 331(d), 355(a)-(d); S. Rep. 1744, 87th Cong., 2d Sess. Pt. 2, at 4-5 (1962); 108 Cong. Rec. 17,366 (1962) (statement of Sen. Eastland).

The new drug approval requirements in effect today thus reflect two related and reasonable conclusions that Congress and the FDA drew from long experience with drug regulation. First, proof of the safety and effectiveness of a new drug must be established by rigorous, scientifically valid clinical studies rather than the impressions of individual doctors, who cannot by themselves compile and master the necessary information; and, second, a premarket approval requirement is necessary to ensure that those who promote and distribute new drugs, and seek to realize profits from their distribution, undertake the investigations necessary to establish effectiveness and safety. See Hynson, Westcott & Dunning, 412 U.S. at 619, 629-630; Warner-Lambert Co., 787 F.2d at 156. For these reasons, the new drug approval process is a critical component of the FDCA's regulatory framework for the protection of the public health and safety. As the district court and court of appeals both concluded (Pet. App. 5a-6a, 40a-41a), there is a substantial governmental interest in preserving the integrity of that process.

2. There is a substantial governmental interest in ensuring the availability of compounding in response to individual medical needs

At the same time that Congress sought, through the new drug approval process, to protect the public from unsafe and ineffective drugs, Congress recognized that it is also important to ensure that drug treatments that are safe and effective are in fact available. Congress therefore carefully crafted the new drug approval process "to insure that governmental control does not become so rigid that

the flow of new drugs to the market, and the incentive to undergo the expense involved in preparing them for the market, become stifled." S. Rep. No. 1744, supra, Pt. 1, at 14-15; see id. at 16; H.R. Rep. No. 2139, 75th Cong., 3d Sess. 823 (1938); Hynson, Westcott & Dunning, 412 U.S. at 639 n.2 (Powell, J., concurring) (noting the public interest "in protecting the drugs that are useful in the prevention, control, or treatment of illness").

Congress also has generally refrained from providing in the FDCA for the FDA to limit a physician, as part of the practice of medicine, from prescribing any legally available product for a particular patient. See 37 Fed. Reg. 16,503 (1972) (noting repeated references in the legislative history of the 1938 Act and the 1962 amendments that Congress did not intend the FDA to interfere with a physician's ability to prescribe legally approved products for unapproved uses); e.g., S. Rep. No. 361, 74th Cong., 1st Sess. 3 (1935); H.R. Rep. No. 2755, 74th Cong., 2d Sess. 5 (1936); S. Rep. No. 1744, supra, Pt. 1, at 56 (views of Sens. Dirksen and Hruska). Consistent with that background, the FDA has permitted physicians to prescribe approved drugs for uses that are not identified in approved labeling. See 12 FDA Drug Bulletin 4-5 (1982); J.M. Beck & E.D. Azari, FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions, 53 Food, Drug, & Cosm. L.J. 71, 76-79 (1998). That policy reflects the FDA's recognition that certain off-label uses perform an important therapeutic role in certain areas of medical practice, and that undue restrictions on such uses could have adverse health consequences. See id., at

79-80; cf. Buckman Co. v. Plaintiffs' Legal Comm., 121 S. Ct. 1012, 1018-1019 & n.5 (2001) (discussing off-label uses prescribed or administered by physicians in the context of the FDCA's device provisions). The FDA has followed that policy even though manufacturers and distributors may not distribute approved products for off-label uses -- and therefore may not promote off-label uses -- without first demonstrating to the FDA that the products are safe and effective for those uses and obtaining FDA approval. 12 FDA Drug Bulletin 4, 5.

Similar considerations led the FDA to refrain from taking enforcement action against pharmacists who compounded drugs in response to valid prescriptions to meet the medical needs of individual patients, as determined by their physicians, even though introduction of compounded drugs into interstate commerce without FDA approval was illegal before enactment of Section 353a in 1977. See pp. __, supra. The FDA recognized that compounding in response to a valid prescription to meet individual medical needs is a traditional element of the practice of pharmacy. Pet. App. 71a; see also L.V. Allen, Jr., The Art, Science, and Technology of Pharmaceutical Compounding xvi, 1 (1998); C.M. Wyandt & J.S. Williamson, Compounding: Regulatory and Management Issues, Drug Topics, July 1999, at 43.[2]

[2] See also Virginia State Bd. of Pharm. v. Virginia Citizens Consumer Council, Inc., 425 U.S. 748, 752, 766 (1976) (noting that, in the mid-1970s, approximately 5% of prescriptions were compounded by pharmacists); S.H. Kalman & J.F. Schlegel, Standards of Practice for the Profession of Pharmacy, NS19 No. 3 American Pharmacy 29 (1979) (discussing pharmacists' compounding responsibilities); Complaint ¶ 20 reprinted in C.A. Excerpts of Record (hereinafter C.A. E.R.) 5 ("Pharmacy compounding is a time-honored, customary and traditional part of pharmacy practice. It is a mandatory subject in most pharmacy schools. Most, if not all, state laws require that pharmacists be proficient in compounding and that they maintain special compounding equipment.").

Like certain off-label uses, compounding in response to individual medical needs may have important health benefits. It allows physicians and pharmacists to work together to develop customized therapies for patients for whom commercially manufactured drugs are not suitable for various medical reasons. For example, when a patient has an allergy to a component of a commercially available product, or an approved drug does not come in a dosage appropriate for an individual or in a delivery system that the patient can tolerate, the physician and pharmacist can work together to create a compounded product that addresses the patient's particularized needs. See Professionals & Patients for Customized Care v. Shalala, 56 F.3d 592, 593 (5th Cir. 1995); Pet. App. 41a-42a.[3]

Of course, it might theoretically be ideal if a pharmacy first demonstrated to the FDA that a compounded drug is safe and effective for its intended use before it is sold to an individual

[3] See also C.A. E.R. 6 (giving examples of the benefits of compounding); K. Ranelli, Extending the Family, The Hartford Courant, Mar. 16, 2000, at E1 ("Compounding can include making a natural, bio-identical drug for hormone therapy, changing an oral medication into a topical cream for patients who can't swallow easily, and tailoring drugs to children's taste by adding a fruit extract."); H. Dukes, Compounding of Medications Enjoys a Comeback, South Bend Tribune, Jan. 31, 2001, at C1 (benefits of compounding include pediatric dosages of drugs manufactured only for adults and providing medications that drug companies no longer make).

patient. However, because obtaining FDA approval of a new drug is a costly process, requiring FDA approval of all drug products compounded by pharmacies for the particular needs of an individual patient would, as a practical matter, eliminate the practice of compounding, and thereby eliminate availability of compounded drugs for those patients who have no alternative treatment. The cost of developing and obtaining approval of a new drug that is not closely similar to an already approved drug is generally estimated to exceed $200 million dollars. See Henry, supra, at 617; J.A. Henderson, Jr. & A.D. Twerski, Drug Designs Are Different, 111 Yale L.J. 151, 164-165 (2001). The cost of developing drugs that closely resemble approved products is still substantial -- ranging from $300,000 to $500,000. See Balaji K., Generics: The Opportunity Beckons (July 2001) <http://www.inpharm.com/intelligence/frost010701.html>.

Just as those costs have discouraged manufacturers from developing drugs to treat rare illnesses, see Henry, supra, at 628-630, the high costs of the approval process would make it uneconomical for a typical pharmacist to obtain approval for a drug that is compounded for a limited number of people - sometimes only a single individual - for whom the product is medically necessary. Requiring approval in those circumstances would not be feasible, and advance approval of such individual compounded drugs is less central to protecting the broader public health than is the advance approval of products that are distributed more widely to the public. The FDA's policy of not enforcing the new drug approval

requirements against traditional pharmaceutical compounding was thus a reasonable exercise of informed regulatory enforcement discretion based on the conclusion that there is a substantial governmental interest in permitting compounding in response to the particularized medical needs of identified individuals -- a conclusion with which the district court and court of appeals in this case did not disagree (Pet. App. 7a-8a, 42a).

3. There is a substantial governmental interest in balancing the interests in permitting compounding in response to individual medical needs and protecting the integrity of the new drug approval process

a. Although there are benefits from drug compounding in appropriate individualized circumstances, experience under the FDA's enforcement policy prior to 1997 showed that compounding can also present significant health and safety risks. Some pharmacies were compounding outside the scope of normal pharmacy practice and were mass-producing and distributing compounded drugs in a manner tantamount to the manufacture of new drugs. Pet. App. 72a. Compounding on that scale exposed substantial numbers of the public to the kinds of risks that had led to the enactment of the new drug approval process in the first place. For example, some drug products compounded by pharmacies contained impurities that caused serious injuries, such as eye infections that required removal of patients' eyes, and fatalities, including deaths of infants. Id. at 73a; T. Nordenberg, Pharmacy Compounding: Customizing Prescription Drugs, 34 FDA Consumer No. 4, at 11 (2000); C.E. Myers, Needed: Serious Attention to Sterile Products, 53 Am. J. Health Sys. Pharm. 2582 (1996).

Even more significantly, compounding on a scale tantamount to manufacturing was allowing wholesale circumvention of the new drug approval process. Pet. App. 73a-74a. Pharmacies could mass-produce a particular drug product, stimulate demand for the product through advertising, and thereby effectively manufacture and distribute the drug in interstate commerce without complying with the new drug approval requirements. See FDA Reform Legislation: Hearings Before the Subcomm. on Health and the Env't of the House Comm. on Commerce, 104th Cong., 2d Sess. 31, 125 (1996) (FDAMA Hearings) (testimony of Hon. David A. Kessler, Commissioner, FDA); id. at 59 (FDA Analysis); Addressing the FDA's Performance, Efficiency, and Use of Resources: Hearings Before the Senate Comm. on Labor and Human Resources, 105th Cong., 1st Sess. 28 (1997) (testimony of Michael D. Friedman, M.D., and William Schultz, Deputy Commissioners, FDA).

That practice presented far more serious potential consequences than the possibility that small quantities of drugs that might be unsafe or ineffective might be sold by a local pharmacy in individual situations. The practice threatened to undermine the new drug approval process and weaken the very core mission of the FDCA itself. If drug producers could mass-produce drugs through pharmacy entities engaged in widespread compounding, and thus bypass the approval process, manufacturers would have far less incentive to bear the cost of establishing that the drugs they seek to market are in fact safe and effective. See FDAMA Hearings 31, 59; see also D.B. Brushwood, Responsive Regulation of Internet

Pharmacy Practice, 10 Annals Health L. 75, 85-86 (2001) (describing high-volume compounding that occurred in the 1990s as an "unregulated industry of clandestine drug manufacturers"). Cf. Weinberger v. Bentex Pharm., Inc., 412 U.S. 645, 653 (1973) (noting that it would be "inherently unfair" to require compliance by one manufacturer with the new drug approval requirements "while his competitors marketing similar drugs remain free to violate the Act").[4]

Because the FDA recognized the importance of balancing the interest in permitting compounding to meet individual medical needs with the interest in protecting the integrity of the new drug approval process, the FDA, before the enactment of Section 353a in 1997, brought enforcement actions against pharmacies that were engaged in compounding that was tantamount to manufacturing. Pet. App. 73a-74a; see pp. __, supra. When Congress addressed the compounding issue by enacting Section 353a, it sought to achieve essentially the same balance of interests that the FDA had pursued through its enforcement policy. See H.R. Conf. No. 399, 105th Cong., 1st Sess. Rep. 94 (1997) (explaining that Section 353a

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[4] Attempts by drug manufacturers to bypass the new drug approval process are not infrequent. See, e.g., United States v. Sage Pharm., Inc., 210 F.3d 475 (5th Cir. 2000); Florida Breckenridge, Inc. v. Solvay Pharm., Inc., No. 98-4606 (11th Cir. May 11, 1999); United States v. Hiland, 909 F.2d 1114 (8th Cir. 1990); United States v. 50 Boxes More or Less, 909 F.2d 24 (1st Cir. 1990); United States v. Sandoz Pharm. Corp., 894 F.2d 825 (6th Cir. 1990); United States v. 225 Cartons, More or Less, of an Article or Drug, 871 F.2d 409 (3d Cir. 1989); United States v. Atropine Sulfate 1.0 Mg. (Article of Drug) Dey-Dose, 843 F.2d 860 (5th Cir. 1988); United States v. Articles of Drug, 826 F.2d 564 (7th Cir. 1987); Premo Pharm., Inc. v. United States, 629 F.2d 795 (2d Cir. 1980).

"ensure[s] continued availability of compounded drug products as a component of individualized therapy, while limiting the scope of compounding so as to prevent manufacturing under the guise of compounding"); accord S. Rep. No. 43, 105th Cong., 1st Sess. 67 (1997).

b. The court of appeals refused to credit the government's interest in achieving that balance because, in the court's view, the government did not present "convincing evidence" of "the health risks associated with large numbers of patients taking [compounded] drugs." Pet. App. 6a-7a. That evidentiary demand was wholly misplaced. In the first place, this Court has made clear that the government may "justify [advertising and solicitation] restrictions based solely on history, consensus, and 'simple common sense.'" Lorillard Tobacco Co. v. Reilly, 121 S. Ct. 2404, 2422 (2001) (quoting Florida Bar v. Went For It, Inc., 515 U.S. 618, 628 (1995) (citations and internal quotation marks omitted)). As described above, the substantiality of the government's interests here is amply supported by the history of congressional regulation of drug manufacturing, the FDA's regulatory experience with compounding, and "simple common sense." Ibid.

Furthermore, the court of appeals' insistence that the government produce "convincing evidence" in court was particularly inappropriate in this case, because it was based on a rejection of the fundamental premises of the FDCA itself, which in turn reflect decades of agency and congressional experience -- that the widespread distribution of drugs that have not been shown to be

safe and effective poses substantial health risks, and that the FDCA's new drug approval requirements are a legitimate and effective means to address those risks. This Court has acknowledged the validity of those premises, see Rutherford, 442 U.S. at 556-557; Hynson, Westcott & Dunning, 412 U.S. at 619, 622, and the court of appeals had no basis to question them.

The court of appeals' ruling on this point appears to have stemmed from its failure to appreciate the full extent of the government's interest. That interest is not simply, as the court of appeals characterized it, in "preventing widespread compounding." Pet. App. 7a. Rather, as described above, the government's interest is in preventing compounding that is tantamount to manufacturing and therefore undermines the federal scheme for ensuring that drugs are safe and effective before they are introduced into commerce. Congress sought to balance that substantial interest with the substantial but competing interest in making compounded drug products available in circumstances in which they are necessary to meet the particularized medical needs of individual patients and a prior approval requirement generally would not be feasible. See H.R. Conf. Rep. No. 399, supra, at 94; S. Rep. No. 43, supra, at 67; compare Buckman Co., 121 S. Ct. at 1018 (under the FDCA, "the FDA pursues difficult (and often competing) objectives"). Balancing those two goals is a substantial governmental interest in its own right. See United States v. Edge Broad. Co., 509 U.S. 418, 428 (1993) (balancing

competing governmental concerns can be a substantial governmental interest for purposes of the Central Hudson test).

B. Section 353a Directly And Materially Advances The Government's Interests

Although Section 353a seeks to advance the same interests that the FDA previously pursued through the exercise of its enforcement discretion, Congress chose to endorse and lend the strength of its backing to those goals by setting forth in the FDCA itself the "parameters under which compounding is appropriate and lawful." S. Rep. No. 43, supra, at 67. Section 353a thus exempts compounded drug products from the FDCA's provisions governing new drug approval, as well as the provisions concerning good manufacturing practice and adequate directions for use, under certain specified conditions.

The conditions at issue here involve limitations on the solicitation of prescriptions and advertising. Section 353a(a) exempts compounding from the new drug approval and related requirements only if the compounded drug is produced "based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient." 21 U.S.C. 353a(a) (Supp. V 1999). Section 353a(c) further provides that a pharmacy is entitled to the exemption only if it "does not advertise or promote the compounding of any particular drug, class of drug, or type of drug." 21 U.S.C. 353a(c) (Supp. V 1999). The advertising limitation does not, however, prevent the pharmacy from advertising that it performs compounding services generally. 21

U.S.C. 353a(c) (Supp. V 1999). The solicitation and advertising conditions on the application of the exemption directly and materially advance the government's interest in balancing the competing goals of ensuring the availability of compounding in response to particularized medical needs of individual patients and protecting the integrity of the new drug approval requirements.

1. Promotion of particular drugs reasonably distinguishes drug manufacturing that is subject to the premarket approval process from compounding in response to individual medical needs

a. Before enactment of Section 353a, the FDA considered a variety of factors to determine whether a pharmacy was manufacturing under the guise of compounding and thus circumventing the new drug approval requirements in a manner that materially undermined the purposes of the FDCA. See pp. __, supra; Pet. App. 76a-77a. Among those factors was whether the pharmacy was "[s]oliciting business (e.g., promoting, advertising, or using sales persons) to compound specific drug products, product classes, or therapeutic classes of drug products." Id. at 76a. The FDA explained that, in its experience, such practices "are far more consistent with those of drug manufacturers and wholesalers than with retail pharmacies." Id. at 72a. Building on the FDA's experience, Congress found similar considerations useful and appropriate in drawing the line between traditional, individualized compounding and compounding that is tantamount to manufacturing. See 143 Cong. Rec. S9839 (daily ed. Sept. 24, 1997) (statement of Sen. Kennedy); ibid. (statement of Sen. Hutchinson).

As the FDA had previously determined, Congress reasonably concluded that advertising of particular drug products is a business practice that is characteristic of manufacturing but not of traditional compounding by a pharmacy for an individualized need. Traditional compounding involves the provision of a service in response to a physician's prescription and an individual patient's particular medical situation. See Pet. App. 71a-72a; Allen, supra, at xv, 1 (National Association of Boards of Pharmacy defines compounding as the preparation of a drug "as the result of a practitioner's Prescription Drug Order or initiative based on the pharmacist/patient/prescriber relationship."); Wyandt & Williamson, supra, at 43, 49 (same). Compounding is thus responsive: it arises out of "specific practitioner/patient/pharmacist relationships" and "result[s]" from the "practitioner's [p]rescription * * * or initiative." Id. at 49 (emphasis added). Compounding in anticipation of prescription drug orders occurs only based on "routine, regularly observed patterns." Ibid.; Allen, supra, at xv, 1. Compounding produces a medication that is "customiz[ed]" for "the patient's unique needs." A. Joyner, Local Pharmacies Invest In Compounding, Billings Gazette, Feb. 27, 2000, at 1D.[5]

[5] See Dukes, supra, at C1, C2 (describing compounding as providing "tailor-made" medicines); B.H. Thiers, Compounding Is Still Appropriate in Clinical Practice, 16 Dermatologic Clinic No. 2, at 330 (1998) (compounding "allows the physician to individualize treatment to the patient's specific needs"); Allen, supra, at xix (compounding involves providing "patient-specific products"); C.A. E.R. 5 ("It is common in the practice of compounding for a physician, pharmacist, and patient to collaborate to select the proper combination of ingredients, dosage, and method of application or ingestion.").

Advertising the particular products created in the provision of the compounding service (as opposed to advertising the compounding service itself) is not necessary to or characteristic of this type of responsive and customized service. Although advertising is useful in a broad market, it serves little purpose when a medication is compounded in response to an individual and often unique need.

Drug manufacturing is the large scale production of a drug product, typically for a substantial market. Promotion of the manufactured product to physicians or the public is a common feature of drug manufacturing. Pet. App. 72a; K.B. Leffler, Persuasion or Information? The Economics of Prescription Drug Advertising, 24 J.L. & Econ. 45, 46 (1981) (market for prescription drugs is "characterized by very large promotional expenditures"); National Institute for Health Care Management, Prescription Drugs and Mass Media Advertising, 2000, at 4 (Nov. 2001) <http://www.nihcm.org/DTCbrief2001.pdf> ($15.7 billion was spent on promotion of prescription drugs in 2000, including $4 billion for doctor's office detailing, $2.5 billion for direct advertisements to consumers, and almost $500 million for advertisements in medical journals). Successful competition in providing homogenous drug products "requires the identification and knowledge of individual manufacturers," and, thus, advertising typically is critical to successful drug manufacture. Leffler, supra, at 48 (explaining how centralized production of drugs increased the use of manufacturer trademarks and brand-name promotion); see E. Kremers & G. Urdang,

History of Pharmacy 164 (2d ed. 1951) (stating that the rise of the proprietary drug industry was "the product of the extension and perfection of the art of advertising, furthered by the trade-mark acts").[6] Expenditures on such advertising therefore are a fair proxy for actual or intended large-scale manufacturing. Thus, by restricting the compounding exemption to pharmacies that do not engage in the promotional conduct characteristic of manufacturing, Congress rationally calculated that "the exemption would not create a loophole that would allow unregulated drug manufacturing to occur under the guise of pharmacy compounding." 143 Cong. Rec. at S9839 (statement of Sen. Kennedy).

b. Conditioning exemption from the regulatory approval process for compounded drugs on the absence of promotion of those products also reflects the FDCA's underlying premise that the public health is best served when those who develop and promote new drugs prove that those drugs are safe and effective. See Hynson, Westcott & Dunning, 412 U.S. at 619, 629-630; pp. __, supra. If compounders could actively promote specific products through advertising without having to bear the costs of the new drug approval process, they would enjoy an unfair advantage over

[6] See also Allen, supra, at 1 (defining drug manufacturing to include "the promotion and marketing of [the manufactured] drugs"); Wyandt & Williamson, supra, at 6 (same); Administered Prices, Drugs, S. Rep. No. 448, supra, at 157 (noting that "virtually all who attempt to market some trademarked specialties engage in journal advertising, direct mail, and the supplying of free samples to physicians"); J. Avorn et al., Scientific versus Commercial Sources of Influence on the Prescribing Behavior of Physicians, 73 Am. J. of Med. 4, 7 (July 1982) (explaining that "[t]ypically, the initial promotion of a new drug is accompanied by extensive advertisement of its virtues").

traditional drug manufacturers, who must comply with the approval requirements. That unfair advantage would undermine the statutory incentive for drug manufacturers to comply with the approval requirements, which are the FDCA's central mechanism to ensure that drugs introduced into interstate commerce are safe and effective for their intended uses. See pp. __, supra (explaining that manufacturers could by-pass the approval process by establishing pharmacy subcomponents).

c. Advertising and other promotional material have long been critical factors in determining the scope of regulation under the FDCA. For example, the FDA considers labeling, promotional material, and advertising (among other things) to determine whether a substance constitutes a "drug" that is subject to regulation under the Act because it is intended to treat disease or otherwise to affect the structure or function of the body. See 21 U.S.C. 321(g)(1); e.g., United States v. Storage Spaces Designated Nos. "8" and "49" Located at 277 E. Douglas, Visalia, CA, 777 F.2d 1363, 1366-1367 & n.6 (9th Cir. 1985); National Nutritional Foods Ass'n v. Mathews, 557 F.2d 325, 334 (2d Cir. 1977); United States v. Article . . . Consisting of 216 Individually Cartoned Bottles, 409 F.2d 734, 739 (2d Cir. 1969) (collecting cases).

Similarly, promotional representations can be an important indicator of whether a new drug application or supplemental new drug application is required for a product, e.g., as a result of advertising recommending a new use for the product. The labeling for a drug must indicate "all conditions, purposes, or uses for

which such drug is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising." 21 C.F.R. 201.5; see also 21 C.F.R. 201.128 (in determining a drug's intended uses, the FDA considers, among other things, "labeling claims, advertising matter, or oral or written statements" by the persons legally responsible for the product's labeling or their representatives). If a product is labeled for a new intended use, as required by those regulations, it is a "new drug" (for which FDA premarket approval is required), because it is not generally recognized to be safe and effective for use "under the conditions prescribed, recommended, or suggested in the labeling thereof," or, while so recognized, has not been used for a material time or to a material extent under such conditions. 21 U.S.C. 321(p); 108 Cong. Rec. at 17,366 (statement of Sen. Eastland). The use claimed for a drug in promotional material (and otherwise) thus may be an important factor in determining whether or not it is a new drug and whether FDA premarket approval is required. See S. Rep. No. 1744, supra, Pt. 1, at 17; id. at 59-60 (views of Sens. Dirksen and Sen. Hruska); S. Rep. No. 1744, supra, Pt. 2, at 5; see also Hynson, Westcott & Dunning, 412 U.S. at 613, 629, 632 (new drug is one not generally recognized by experts as safe and effective for its "intended use"). Therefore, denying the exemption from the FDA approval requirements when compounded drug products are advertised or otherwise promoted is entirely consistent with the overall structure and administrative implementation of the FDCA.

2. The court of appeals erred in concluding that the advertising and solicitation conditions do not materially advance the government's interests

a. The court of appeals erroneously concluded that limiting the exemption from the premarket approval and other requirements to pharmacies that do not promote particular compounded products does not directly and materially advance the government's interests. Pet. App. 7a-10a. As an initial matter, the court faulted the government for failing to demonstrate that Section "353a's speech restrictions will keep the demand for particular compounded drugs artificially low, and thereby protect unwary consumers." Id. at 8a. Once again, the court of appeals appears to have misunderstood the government's argument and burden. As discussed above, the government's argument is that Congress sensibly concluded that advertising for a particular compounded drug product reasonably identifies the point at which the interest in preserving the integrity of the new drug approval requirements outweighs the interest in protecting the availability of traditional pharmaceutical compounding in response to individual medical needs. That contention in no way requires a showing that Section 353a's speech restrictions will suppress the demand for particular compounded drugs.

The court of appeals also relied on its own assessment that other "safeguards exist to protect the public." Pet. App. 8a. The provisions of Section 353a to which the court referred, however, do not advance the governmental interests underlying that Section. For example, the court noted that, under FDAMA, "[n]o compounded

drug may be dispensed without a valid prescription from a licensed physician." Id. at 8a-9a (citing 21 U.S.C. 355a(a) (Supp. V 1999)). That requirement, however, is insufficient to advance the government's interest in preserving the integrity and safeguarding function of the FDCA's new drug approval process. That process rests on the learning accumulated over decades by the FDA and Congress that the ultimate determination whether a new drug is safe and effective cannot be left to individual doctors, who cannot by themselves compile and master the necessary information, but must be made by the FDA on the basis of scientific evidence submitted by the manufacturer. See Hynson, Westcott & Dunning, 412 U.S. at 619, 630; Warner-Lambert Co., 787 F.2d at 156.

The court of appeals also observed that a "pharmacist cannot regularly compound drugs that are essentially copies of a commercially available drug product." Pet. App. 9a (citing 21 U.S.C. 353a(b)(1)(D) (Supp. V 1999)). Although that limitation does indeed further the government's interest in preventing pharmacies from manufacturing products that are already available without complying with the FDCA's requirements, it does not address the problem of the manufacture through widespread compounding of products that are different from those that are commercially available. That latter form of compounding is addressed by Sections 353a(a) and (c), by ensuring that entities that promote the distribution in interstate commerce of new drug products comply, as must conventional manufacturers, with the new drug approval requirements. By requiring such parity in treatment,

Section 353a preserves the integrity and protective function of the new drug approval process and prevents the widespread distribution of new drugs that have not been proven safe and effective.

Nor do 21 U.S.C. 353a(b)(1)(A) and (B), which limit the substances that pharmacists may use in compounding, adequately address the governmental interest in preventing the manufacturing of new drugs under the guise of compounding. Those provisions require that the ingredients used in compounded products meet certain quality standards, which are less extensive than those that apply to approved products under 21 U.S.C. 351(a)(2)(B) (Supp. V 1999). They do not ensure the safety and effectiveness of the compounded drugs themselves, which are still unapproved new drugs; and they do not operate to prevent compounding activity that is on the scale and in the manner of manufacturing.

b. The Ninth Circuit also concluded that Section 353a fails the third Central Hudson inquiry because, in the court's view, it "is so riddled with exceptions that it is unlikely that the speech restrictions would actually succeed in depressing the volume of compounded drugs." Pet. App. 9a. The court noted, for example, that Section 353a permits pharmacies to advertise their general compounding services (see 21 U.S.C. 353a(c) (Supp. V 1999)) and does not prevent them from dispensing significant quantities of drugs intrastate (see 21 U.S.C. 353a(b)(3) (Supp. V 1999)). Those provisions, however, do not undermine the government's interest in preventing manufacturing under the guise of compounding.

As discussed above, if compounders could actively promote particular compounded drug products without complying with the new drug approval requirements, they would enjoy an unfair advantage over traditional drug manufacturers that would significantly reduce the incentives for manufacturers to expend the resources necessary to prove that their new drugs are safe and effective. Indeed, under such a regime, traditional drug manufacturers could establish compounding entities and circumvent the approval process.

Moreover, advertising of particular drug products is a historical and critical characteristic of drug manufacturing but not of traditional compounding. See pp. __, supra. General advertising that a pharmacy provides compounding services does not suggest the existence, or foster the growth, of a market for any particular compounded drug, and thus does not distort the incentives of drug manufacturers to comply with the new drug approval requirements. Permitting pharmacies to advertise that they provide compounding services therefore is consistent with, not at odds with, Congress's interest in ensuring that drugs are widely distributed in commerce only after they have been proven to be safe and effective for their intended uses. Allowing general advertising of compounding services -- including information about the pharmacist's experience, the timeliness of services, and physician satisfaction -- also promotes Congress's interest in preserving the availability of medically necessary treatments when demand is insufficient to justify the costs of pre-approval. Section 353a thus does not permit "speech that poses the same risks

the Government purports to fear." Greater New Orleans Broad., 527 U.S. at 195.

Nor does 21 U.S.C. 353a(b)(3) (Supp. V 1999) undermine the government's interest. Section 353a(b)(3) provides that a pharmacy may avail itself of the compounding exemption only if it is located in a State that has entered into an agreement with the Secretary that addresses the interstate distribution of inordinate amounts of compounded drugs, or if the pharmacy's total interstate distribution of compounded drug products does not exceed 5 percent of its total prescription orders. See 21 U.S.C. 353a(b)(3) (Supp. V 1999). That provision imposes a restraint in addition to and somewhat different in purpose from the restrictions on advertising and solicitation of prescriptions for individual drugs. The advertising and solicitation limitations prevent the manufacture of particular drug products under the guise of compounding. Section 353a(b)(3) limits the volume of the pharmacy's overall interstate sales of compounded drugs to ensure that the pharmacy retains its general character as a retail pharmacy rather than a drug manufacturer.

The volume limitation in Section 353a(b)(3) applies only to interstate distributions so that the States may continue to play their traditional role in regulating the practice of pharmacy. See 143 Cong. Rec. S12,242 (daily ed. Nov. 9, 1997) (statement of Sen. Jeffords) (Congress intended "to establish a rational framework for pharmacy compounding [that] respects the State regulation of pharmacy while allowing an appropriate role for the FDA"). The

absence of volume limitations on overall intrastate distributions does not, however, undermine the advertising and solicitation restrictions, which continue to prevent compounding of a particular drug that would be tantamount to the manufacturing of new drugs.

C. Section 353a Does Not Burden An Excessive Amount Of Speech In Relation To Its Purposes

The final consideration under Central Hudson is whether the advertising and solicitation limitations in Section 353a are "more extensive than * * * necessary" to serve the governmental interests that they advance. 447 U.S. at 566. As this Court recently reiterated, that inquiry is not a "least restrictive means" test. Lorillard Tobacco Co., 121 S. Ct. 2422 (2001) (quoting Went For It, 515 U.S. at 632). Instead, the First Amendment requires only a "reasonable 'fit between the legislature's ends and the means chosen to accomplish those ends.'" Ibid. (quoting in turn Board of Trs. of State Univ. of N.Y. v. Fox, 492 U.S. 469, 480 (1989)). The limitations in Section 353a satisfy that requirement.

1. The advertising and solicitation limitations are carefully crafted to meet the government's goals

The limitations on advertising and solicitation in Section 353a are not more extensive than necessary to advance the government's goals. Most significantly, Section 353a does not absolutely prohibit any speech. A pharmacy that wishes to mass-produce a particular drug product and promote that product by advertising or soliciting prescriptions can do so -- just as any other drug manufacturer can -- if it complies with the FDCA's new drug approval and related requirements. It is only if the pharmacy

desires to avail itself of the exemption from those otherwise generally applicable requirements on conduct that it must limit its promotional activities. As explained above, if a pharmacy could produce and promote compounded drugs without complying with the new drug approval requirements, the requirements would be substantially undermined. The limitation on promotion is thus well calibrated to the government's interest in protecting the integrity of the new drug approval requirements. Cf. Dolan v. City of Tigard, 512 U.S. 374, 385, 391 (1994) (government may condition a benefit on the relinquishment of a constitutional right if waiver of the right is reasonably related to the benefit) (citing Pickering v. Board of Educ., 391 U.S. 563, 568 (1968) (government may impose limitations on the speech of its employees when justified by its interests as an employer)).

The advertising limitation is also tailored to accommodate the commercial speech necessary to the practice of traditional compounding. Section 353a(c) expressly permits advertising for and promotion of "the compounding service provided by the licensed pharmacist." 21 U.S.C. 353a(c) (Supp. V 1999). Therefore, compounders may, consistent with FDAMA, advertise that they perform compounding services, that they are experts in compounding, and that they stand ready to fill prescriptions for compounded drug products. They may also advertise other information that relates to their general compounding practice, such as the mark-up that they charge in exchange for their compounding services. This kind of advertising is consistent with the government's interest under

FDAMA in ensuring the availability of compounding in response to individual medical needs without undermining the integrity of the new drug approval process. See pp. __, supra. Advertising of particular compounded drugs, in contrast, is not necessary to the practice of traditional compounding and would permit compounding pharmacists to engage in manufacturing and thus threaten the integrity and safeguarding function of the new drug approval requirements. See pp. __, supra.

The solicitation provisions are also narrowly drawn. Section 353a(a)(2) permits compounding "in limited quantities" before the receipt of a valid prescription for a particular patient if the decision to compound is based on an established relationship among the pharmacist, the practitioner, and the patient. 21 U.S.C. 353a(a)(2) (Supp. V 1999). That provision accords with the traditional practice of compounding, as defined by the National Association of Boards of Pharmacy. See Allen, supra, at xv (compounding is the preparation of a drug "as the result of a practitioner's Prescription Drug Order or initiative based on the pharmacist/patient/prescriber relationship," but "also includes the preparation of drugs * * * in anticipation of Prescription Drug Orders based on routine, regularly observed patterns").

As the court of appeals noted, the FDA interprets Section 353a(a) to permit a pharmacist to "call a physician and recommend a drug compound when a patient comes in with a prescription for a commercial drug and provides information to the pharmacist that indicates that the patient might require a compounded product."

Pet. App. 9a; see also C.A. E.R. 153. That interpretation derives from the language in Section 353a(a) that permits preparation of a compounded drug based on "a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient." 21 U.S.C. 353a(a) (Supp. V 1999). The FDA's reasonable interpretation of that language is not, as the court of appeals viewed it (Pet. App. 9a), an exception that undermines the ability of Section 353a to achieve the government's goals. It is instead an example of how Section 353a is narrowly tailored. The pharmacist undertakes the permitted activity in response to the particularized medical needs of an identified patient in the context of an existing practitioner/patient/pharmacist relationship. The activity therefore does not pose a significant danger that the pharmacist is engaging in drug manufacturing, but rather fits squarely within the traditional practice of pharmacy compounding. See pp. __, supra (explaining that traditional compounding customizes medications in response to a patient's special needs and based on a relationship among the pharmacist, the patient, and the prescribing physician).

2. The alternatives suggested by the court of appeals would undermine the government's interests

The court of appeals mistakenly believed that "clear alternatives exist that can advance the government's asserted interest in a manner far less intrusive to the pharmacists' free speech rights." Pet. App. 10a. In fact, the alternatives suggested by the court of appeals -- "disclaimers on compounded drugs explaining that they had not been subject to FDA approval,"

or subjecting all compounded drug products to the FDCA's new drug approval requirements, ibid. -- not only would fail to advance, but would actually undermine, the government's interests.

Reliance on disclaimers is inconsistent with the FDCA's premarket approval process. That regime prohibits the interstate distribution of drugs that the FDA has not found to be safe and effective. Congress has determined that public health and safety are best ensured by requiring manufacturers to establish to the FDA that their drugs are safe and effective for their intended uses before they are distributed widely in commerce. See Hynson, Westcott & Dunning, 412 U.S. at 619, 630; pp. __, supra. That determination is amply supported by Congress's experience over the course of the last century in regulating the manufacture of drugs. See pp. __, supra. Disclaimers would not prevent widespread distribution of drugs that have not been demonstrated to be safe and effective. They thus would not provide a satisfactory alternative for the new drug approval regime that Congress, based on many years of experience, reasonably determined to be necessary to protect the public.

The other alternative suggested by the court of appeals -- subjecting all compounded drugs to the new drug approval process -- would undermine Congress's competing goal of making compounded drugs available in the limited circumstances in which a compounded product is necessary to meet an individual patient's medical needs. As described above, because those circumstances are so limited, and the costs of the premarket approval process are usually so

substantial, requiring compliance with the new drug approval requirements in all cases would effectively eliminate the availability of compounded products to meet individual medical needs. See pp. __, supra.

The court of appeals therefore erred in concluding that Section 353a is not narrowly tailored to achieve the government's substantial interest in balancing the availability of compounding in response to the particular medical needs of individual patients with preventing compounding that is tantamount to manufacturing, which would threaten the integrity of the new drug approval requirements.

CONCLUSION

The judgment of the court of appeals should be reversed, and the case should be remanded with instructions to enter judgment for the petitioners.

Respectfully submitted.

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